OPEN ACCESS

KING'S College LONDON

King's Research Portal

DOI:
10.1111/jce.14111

Document Version
Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):
Chubb, H., Karim, R., Mukherjee, R., Williams, S. E., Whitaker, J., Harrison, J., Niederer, S. E., Staab, W., Gill, J., Schaeffter, T., Wright, M., O'Neill, M., & Razavi, R. (2019). A comprehensive multi-index cardiac magnetic resonance-guided assessment of atrial fibrillation substrate prior to ablation: prediction of long-term outcomes. *Journal of Cardiovascular Electrophysiology*, *30*(10), 1894-1903. https://doi.org/10.1111/jce.14111

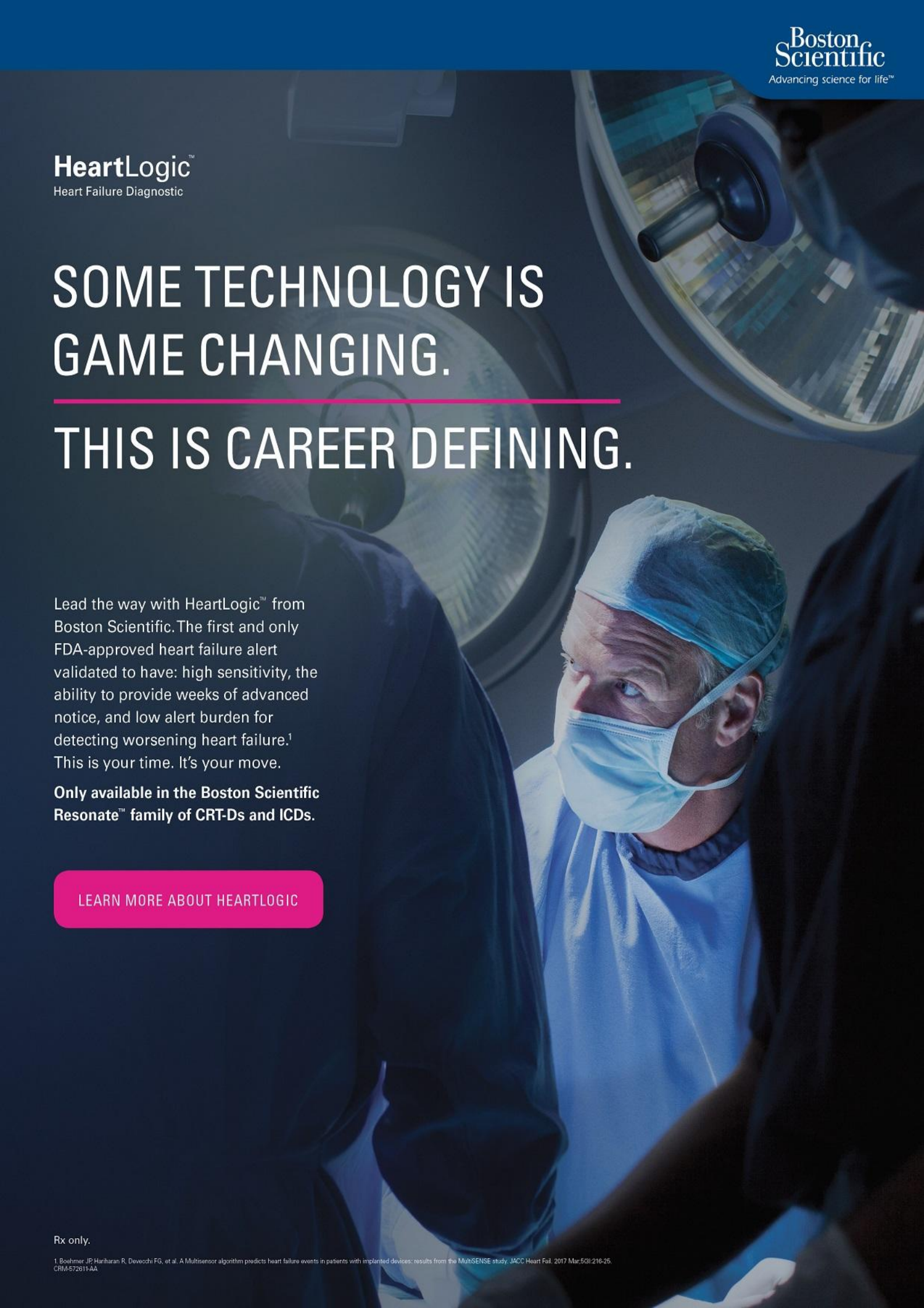
Citing this paper
Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights
Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

•Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
•You may not further distribute the material or use it for any profit-making activity or commercial gain
•You may freely distribute the URL identifying the publication in the Research Portal

Take down policy
If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 06. May. 2023


Boston Scientific
Advancing science for life™
HeartLogic™
Heart Failure Diagnostic
SOME TECHNOLOGY IS GAME CHANGING.
THIS IS CAREER DEFINING.
Lead the way with HeartLogic™ from Boston Scientific. The first and only FDA-approved heart failure alert validated to have: high sensitivity, the ability to provide weeks of advanced notice, and low alert burden for detecting worsening heart failure.[1] This is your time. It's your move.
Only available in the Boston Scientific Resonate™ family of CRT-Ds and ICDs.
LEARN MORE ABOUT HEARTLOGIC
Rx only.
1. Boehmer JP, Hariharan R, Devecchi FG, et al. A Multisensor algorithm predicts heart failure events in patients with implanted devices: results from the MultiSENSE study. JACC Heart Fail. 2017 Mar;5(3):216-25.
CRM-572611-AA

Accepted Article

Henry Chubb ORCID iD: 0000-0002-2859-3536

Steven Williams ORCID iD: 0000-0002-7266-2084

John Whitaker ORCID iD: 0000-0002-5361-5725

A comprehensive multi-index cardiac magnetic resonance-guided assessment of atrial fibrillation substrate prior to ablation: prediction of long-term outcomes

Short Title

Comprehensive CMR-guided AF Substrate Assessment

Authors

Henry Chubb[1] MBBS MA PhD, Rashed Karim[1] PhD, Rahul Mukherjee[1] MBBS, Steven E Williams[1,2] MBBChir PhD, John Whitaker[1] BM BChir MA, James Harrison[1,2] MBBChir PhD, Steven E Niederer DPhil, Wieland Staab[1] MD, Jaspal Gill[1] MBBS, Tobias Schaeffter[1] PhD, Matthew Wright[1,2] MBBS PhD, Mark O'Neill[1,2] MBBCh BAO DPhil FHRS, Reza Razavi[1] MBBS MD

Affiliations

[1]Division of Imaging Sciences and Biomedical Engineering, King's College London, UK

[2]Department of Cardiology, St Thomas' Hospital, London, UK

Corresponding Author

Dr Henry Chubb, Division of Imaging Sciences and Biomedical Engineering, St Thomas' Hospital, London, SE17EH, UK

henry.chubb@kcl.ac.uk, +442071885440

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.14111.

This article is protected by copyright. All rights reserved.

Accepted Article

Financial Support

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London, by the NIHR Healthcare Technology Co-operative for Cardiovascular Disease at Guy's and St Thomas' NHS Foundation Trust, and by the Cardiovascular HTC.

Disclosure Statement

The authors state that they have no conflict of interest to declare

Abstract

Introduction

Multiple CMR-derived indices of atrial fibrillation (AF) substrate have been shown in isolation to predict long-term outcome following catheter ablation. Left atrial (LA) fibrosis, LA volume, LA ejection fraction (EF), LVEF, LA shape (sphericity) and pulmonary vein anatomy have all been shown to correlate with late AF recurrence. This study aimed to validate and assess the relative contribution of multiple indices in a long-term single-center study.

Methods and Results:

89 patients (53% PAF, 73% male) underwent comprehensive CMR study prior to first-time AF ablation (median follow-up 726days (IQR 418-1010days)). 3D LGE acquisition (1.5T, 1.3x1.3x2mm) was quantified for fibrosis, LA volume and sphericity assessed on manual segmentation at atrial diastole, LA and LV ejection fraction (EF) quantified on multi-slice cine imaging.

This article is protected by copyright. All rights reserved.

AF recurred in 43 patients (48%) overall (31 at one year). In the recurrence group, LA fibrosis was higher (42% vs 29%, HR 1.032, p=0.002), LAEF lower (25% vs 34%, HR 0.063, p=0.016) and LVEF lower (57% vs 63%, HR 0.011, p=0.008). LA volume (63 vs 61 ml/m2) and sphericity (0.819 vs 0.822) were similar. Multivariate Cox regression analysis was adjusted for age and sex (model 1), additionally AF type (model 2) and combined (model 3). In models 1 and 2, LA fibrosis, LAEF and LVEF were independently associated with outcome, but only LA fibrosis was independent in model 3 (HR 1.021, p=0.022).

Conclusions:

LAEF, LVEF and LA fibrosis differed significantly in the AF recurrence cohort. However, on combined multivariate analysis only LA fibrosis remained independently associated with outcome.

Key Words

Atrial fibrillation, cardiac magnetic resonance imaging, structural remodeling, atrial fibrosis, catheter ablation

Introduction

Catheter ablation is an effective treatment for appropriately selected patients with atrial fibrillation (AF) [1]. What constitutes appropriate selection, however, remains poorly understood and vigorously debated. CMR permits assessment of left atrial (LA) structural remodeling (SRM), and consequent associated likelihood of procedural success. Several CMR-derived indices of LA SRM have been proposed and validated in isolated studies, but the interaction and additive value of these indices has not been established. The following CMR-derived indices were hypothesized to be independently predictive of outcome following ablation:

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

(i) *Pre-ablation LA fibrosis quantification*. Late gadolinium enhanced (LGE) imaging of the atrial wall, generally accepted to represent intramural fibrosis, is the most widely researched index of LA SRM [2–4], but the reliability of implementation between centers is controversial[5]. An independently derived quantification method, based on an image intensity ratio [4], was developed for this study.

(ii) *LA size*. CMR imaging may be used to assess atrial volume, calculated from multi-slice cine imaging or segmentation of a 3D volumetric dataset, and has been shown to be associated with long-term AF recurrence [6,7].

(iii) *LA function*. LA systolic function is challenging to quantify on echocardiographic imaging, but is relatively reliably assessed on CMR imaging. LA total ejection fraction (LAEF) has been found on multivariate analysis to be independently associated with outcome, and was therefore included as the index of LA function [8].

(iv) *Left ventricular (LV) function*. AF may be both a cause and effect of LV systolic dysfunction and has also been shown to be associated with an increased risk of AF recurrence in some, but not all, studies [6,9].

(v) *LA shape*. Bisbal et al [10] defined an LA sphericity index, derived through quantitative comparison of the segmented LA body (defined on an ungated CMR angiogram) to a sphere, which was found to be strongly predictive of AF recurrence.

(vi) *Pulmonary venous (PV) anatomy*. PV anatomy is reliably identified on CMR imaging and it has been shown that there is a reduced risk of recurrence in those with a single left sided PV (13% versus 34%) [11].

This study aimed to combine the key CMR-derived indices in a detailed assessment of their relative reliability and independence of predictive value, with an aim to create a

This article is protected by copyright. All rights reserved.

Accepted Article

single, weighted, model for testing in future cohorts. The study was performed within a single center real-world environment with long term (2 year) follow-up.

Methods

Patients

Patients planned for first-time AF ablation procedure were referred for pre-procedural clinical CMR scan, from January 2014 to October 2015. Paroxysmal (PAF) and persistent AF (PersAF) were defined as per HRS/EHRA guidelines [1]. Patients who underwent subsequent cryoablation (n=1) or did not receive gadolinium-based contrast agent (n=2, one previous allergic reaction, one patient choice) were excluded. Patients were included regardless of rhythm at the time of scan.

CMR imaging acquisition

CMR imaging was performed on a 1.5T MR-scanner (Ingenia, Philips Healthcare, Best, Netherlands). Cine imaging was performed in end-expiration using a standard multislice bSSFP technique (effective TR 2.7msec, TE 1.3msec, 1.25x1.25mm^2 in-plane, slice thickness 10mm, 50 phases). The 3D inversion recovery spoiled gradient echo (LGE) acquisition was performed with coverage to include the whole of the LA in axial orientation. (TR 5.5msec, TE 3.0msec, flip angle 25° low-high k-space ordering, respiratory and ECG gated (end atrial diastole, maximum 120msec window), 1.3x1.3x4mm^3 acquired resolution with 2mm slice overlap, SPIR fat suppression).

Fibrosis assessment

Analysis was performed on an MITK-based platform (German Cancer Research Centre, Heidelberg, Germany), with custom-build modifications to enable the quantification of atrial fibrosis. The LA endocardial surface was defined via manual

This article is protected by copyright. All rights reserved.

Accepted Article

segmentation within the 3D LGE volume. A 2mm surface dilation was used to define the epicardial border, in keeping with established methods [4], and a mean intensity projection technique was used to ascribe a single signal intensity value to each point on the LA endocardial surface model. The mitral valve, distal PVs (2mm distal to antrum) and LA appendage were removed using Paraview (Clip filter, Kitware, New York, NY, USA) and the surface was re-extracted as a binary file (Figure 1A and B). Further details are available in the online supplement (Supplementary Figure 1).

LA scar burden was quantified using an image intensity ratio threshold (0.97 times mean blood pool (BP) signal intensity (SI) [4]). BP SI was measured for a 4ml spherical volume placed in the center of the LA blood pool, distant from potential artefacts including respiratory navigator induced inflow signal. For reproducibility assessment, 43 LGE volumes were re-segmented independently by a separate observer (WS) and quantified using the same technique.

Left atrial size

LA size was assessed in atrial diastole at maximum volume. The LA was manually segmented from the 3D LGE volume, excluding the LAA and PVs. The volume of the segmentation was assessed using ITK-snap (Version 3.4.0, University of Pennsylvania, USA). For reproducibility assessment, 45 LGE volumes were re-segmented independently by a separate observer (WS).

Left atrial and left ventricular function

LA and LV function were assessed on multi-slice short-axis cine imaging stack, using a conventional manual chamber contouring technique (ViewForum (Philips Healthcare, Best, Netherlands)). The LA was manually contoured at maximum volume (LAV_{max} (end atrial diastole)), and minimum volume (LAV_{min} (end atrial

This article is protected by copyright. All rights reserved.

Accepted Article

systole)), with the LAA and PVs excluded. LAEF was defined as total LA emptying fraction ((LAV_{max}-LAV_{min})/LAV_{max}). For patients in AF during the scan, the minimum and maximum volume time phases were manually selected and assessed. For reproducibility assessment of LA function, 45 patients underwent independent measurement by a separate observer (JG). Reproducibility was not assessed for LVEF.

Atrial sphericity

LA sphericity was calculated according to the methods of Bisbal and co-workers (2013) [10]. The LA body was manually segmented on the 3D LGE acquisition on a slice-by-slice basis on the MITK platform, excluding the LAA and PVs. A VTK shell was created from the segmentation, and sphericity quantification performed using the algorithms published by the Barcelona group [10] (Figure 1C). For reproducibility assessment, 45 LGE datasets were re-segmented by an independent observer (WS).

Pulmonary venous anatomy

PV anatomy was assessed on the 3D LGE dataset. They were classified as normal (2 left and 2 right veins), single left (with any combination of right sided veins), isolated three right sided veins (with 2 left sided veins), or any other pulmonary venous arrangement.

Atrial fibrillation ablation procedure

Two experienced operators performed all procedures under general anaesthesia using Carto3 (Biosense Webster/Johnson&Johnson, New Jersey, USA) electroanatomic mapping system, with the exception of 8 procedures performed using EnSite Velocity (St Jude Medical, St Paul, Minnesota, USA). For patients with a diagnosis of PAF and in sinus rhythm, a point-by-point wide area circumferential ablation (WACA)

This article is protected by copyright. All rights reserved.

Accepted Article

achieving PV isolation (PVI) was performed using 8Fr irrigated SmartTouch catheter (Biosense Webster), or 8Fr irrigated TactiCath catheter (St Jude). Target ablation parameters were >5g for at least 15 seconds per RF delivery location. Power was 30W throughout except on the posterior wall, where it was limited to 25W. Procedural endpoint was defined as PV isolation as confirmed on entry block (and exit block if capture achieved). Adenosine was not used routinely to test isolation and waiting time of 30 minutes after final PV isolation was respected in all patients. For patients presenting with PersAF, a WACA was performed followed by additional ablation lesion sets (mitral line, roof line, inferior posterior line, complex fractionated electrogram ablation) as a step-wise ablation [12]). Overall, 27 had a roof line (4 with incomplete block), 18 a mitral line (one with incomplete block), 12 a low posterior line (one with incomplete block), and 9 had further CFAE ablation. If AF converted to atrial tachycardia, this was mapped using conventional electroanatomic and entrainment techniques and ablation targeted to the arrhythmia mechanism. If AF terminated to sinus rhythm, no further ablation was performed other than to confirm PVI and linear conduction block.

All patients who underwent ablation had failed at least one antiarrhythmic drug prior to ablation. For patients taking antiarrhythmic medication up to shortly before ablation (73 patients, 82%), the drug was continued up to 3 months post ablation. Final medications prior to ablation included betablocker for 43 subjects (48%, most commonly bisoprolol), calcium channel blocker (7 (8%)), type 1c sodium channel blocker (19 (21%) most commonly flecainide), sotalol (9 (10%)), digoxin (4 (4%)), and amiodarone (11 (12%)), with 20 patients on >1 antiarrhythmic. For patients who had discontinued ineffective antiarrhythmic medication prior to ablation, further

This article is protected by copyright. All rights reserved.

Accepted Article

medication was only prescribed in the event of an arrhythmia recurrence following ablation.

Subject follow-up

Recurrence of AF post-ablation was defined as a recurrence of AF (>30seconds), or episodes of atrial tachycardia or atrial flutter, in line with HRS/EHRA guidelines [1]. Follow-up was at 3months post-ablation, with symptom review, 24 hour tape and 12-lead ECG performed. Subsequently, patients were typically reviewed at 6 and 12months after the index procedure, and yearly thereafter. A 12-lead ECG ± Holter monitor was performed at each review, in the absence of reported symptoms. If symptoms were reported, patients underwent 12-lead ECG, Holter monitor or event monitor assessment, according to symptom frequency. Patients without recurrence were censored at the time of the last available follow-up and a blanking period of three months was employed post ablation. In the presence of continued arrhythmia recurrence outside of the blanking period, the timing of recurrence was dated to the earliest documented arrhythmia post-ablation.

Statistics

Normally distributed continuous variables are presented as mean ± standard deviation, and median with interquartile range (IQR) for non-normal distribution or non-continuous ordinal data. Time to AF recurrence was related to the individual demographic and CMR covariates using separate univariable Cox proportional hazard regression models. Primary analyses were performed to censoring at one year, or at the date of last contact for those patients who were lost to follow-up prior to day 365. Kaplan-Meier survival curves were compared using Mantel-Cox test with analyses including each patient's complete follow-up period. Where there were no clear

This article is protected by copyright. All rights reserved.

Accepted Article

grounds for dichotomization of an index, high and low index populations were defined arbitrarily at above and below the median respectively. Multivariate Cox proportional-hazards models were used to assess the association of pre-determined indices against arrhythmia recurrence, and results are presented as hazard ratio (HR) with 95% confidence interval. Two initial models were employed, adjusting for age and sex (Model 1) and age, sex and AF type (paroxysmal versus non-paroxysmal AF, Model 2). A final stepwise multivariate model (Model 3) was adjusted as for Model 2 and used all indices with $p<0.05$ in Model 2. Graphical assessment of Schoenfeld Residuals and log-log plots was used to exclude time-dependency of co-variates and violation of proportional hazards assumption. For receiver operator characteristic curves, outcomes were censored at 6months, 1 year and 2 years, and binomial logistic regression performed at 6months only. Statistics were analysed using SPSS Statistics (Version 25, Armonk, NY) and Stata (Version 15.1, Statacorp).

Ethics

All pre-ablation CMR studies were clinically indicated, and ethical approval for retrospective analysis was obtained (REC reference 09-H0802-78).

Results

Patients

In total, 89 subjects underwent full CMR prior to routine first-time ablation, and baseline demographics and associated hazard ratios for AF recurrence are detailed in Table 1. Median total follow-up time was 726 days (IQR 418-1010days), and there were 43 (48%) recurrences by final follow-up, at median 150 days (IQR 79-378days). Two patients were lost to follow-up prior to 6 months post ablation (at 165 and 175 days respectively, no recurrence) and a further 10 patients prior to one year post ablation (at 184, 188, 190, 245, 253, 256, 285, 301, 325 and 334 days respectively, no

This article is protected by copyright. All rights reserved.

recurrence). Kaplan-Meier survival curves for baseline parameters are presented in Supplementary Figure 2. CMR imaging was completed for all subjects for all indices, with the exception of three subjects for whom atrial fibrosis could not be assessed (poor myocardial nulling in two, and unacceptable artefact in one).

CMR-derived indices

CMR-derived indices are summarized in Table 2, and associated Kaplan-Meier plots shown in Figure 2.

The simplest, separate, multivariate analyses of the indices (Model 1) adjusted for age and sex alone, whilst Model 2 additionally adjusted for AF-type (binary: PAF/non-PAF). For both models, atrial fibrosis, LAEF and LVEF were all independently associated with recurrence (Table 3). In Model 3, the combined multivariate analysis of those three significant indices, atrial fibrosis was the only factor independently associated with recurrence (HR 1.021, p=0.022). Detailed analysis of index collinearity and confounding variables is presented in the online supplement (supplementary Figures 3-5 and supplementary Table 2). In total, 36 subjects were imaged in AF, and for these patients functional parameters were significantly reduced [LAEF: 20±11% versus 38±15% (p<0.0001), LVEF: 55±9% versus 64±10% (p=0.0002)], whilst there was no significant difference in LA fibrosis [37±17% versus 31±20%, p=0.16]. The univariate analysis of each parameter in sinus rhythm and AF respectively are presented in Supplementary Table 1. There was no clinically relevant correlation between degree of severity of LA fibrosis or LAEF and time to recurrence (R^2=0.0004 and 0.010 respectively).

Reproducibility of the CMR-derived indices was also assessed, and the results are presented in full in the online supplement (Supplementary Figure 5). Interobserver

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

Lin's concordance correlation coefficients were 0.866 (95% CI 0.787-0.917) for LA fibrosis, 0.923 (95% CI 0.873-0.954) for indexed LA volume, 0.860 (95% CI 0.779-0.912) for LAEF and 0.906 (95% CI 0.842-0.945) for sphericity.

Predictive value

Figure 3 shows receiver operator characteristic curves for the five CMR indices, with outcomes censored at 6 months (26 recurrences in total). A binomial logistic regression was performed to ascertain the combined effects of the CMR parameters (atrial fibrosis, LAEF, LVEF, indexed LA volume) on the likelihood of arrhythmia recurrence; sphericity was excluded to avoid overfitting of the data. The logistic regression model was statistically significant, $\chi^2(4)= 12.5$ ($p=0.014$) and explained 19% (NagelKerke R^2) of the variance in arrhythmia recurrence, correctly classifying 79% of cases (Table 4). Area under the curve (AUC) at 6months was 0.711. The predictive value of each index shifted with time, and ROC curves for each index at 1 year and 2 years are presented in Supplementary Figure 6; AUC for the combined model was 0.780 at 1 year and 0.760 at 2 years.

Discussion

The long-term outcome following AF ablation is excellent in selected patients, but for others the outcome remains suboptimal and improved patient selection may increase interventional success rates. Multiple CMR indices have been shown to be associated with long-term outcome but their implementation in parallel has never been demonstrated. Furthermore, many CMR studies have excluded patients in AF, the very group that stands to benefit most from accurate stratification. This study has taken a real-world cohort of first-time AF ablation patients, and performed follow-up for a median 2 years. The key findings are:

This article is protected by copyright. All rights reserved.

Accepted Article

1. LA fibrosis is independently associated with long-term outcome, as assessed by arrhythmia recurrence
2. LAEF, LVEF and indexed LA volume are significantly associated with outcome, but the associations are not independent
3. LA sphericity, using the assessment methods of this study, is not associated with outcome.

Comparison with prior studies

LA fibrosis has been proposed as a powerful risk stratification modality for patients under consideration for AF ablation. However, implementation of the technique outside of centers in Utah and Johns Hopkins [2,3,13] has been limited, and widespread adoption of the technique has been hindered by the requirement for imaging specialists and image processing teams using bespoke software and considerable experience [1,3,5]. This study has implemented a relatively streamlined approach in the assessment of LA fibrosis, aiming to replicate a mainstream image thresholding technique [4] using tools that can be made freely available to other centers. LA fibrosis scores in this study are similar to those found by the Johns Hopkins group (33.5±18.8% and 35.9±14.8% respectively), as was the hazard ratio per % increase in fibrosis in this study (1.032, 95% CI 1.013-1.052, versus 1.05 [4]).

LAEF, LVEF and indexed LA volume have been shown to be associated with outcome in other studies [6,7,14]. In this combined assessment, the associations were replicated, but they were not shown to be independent. To some extent, the findings here are in concordance with the recent findings of den Uijl and colleagues[7]: on assessment of a more limited set of CMR parameters (LA fibrosis, LA size and LA sphericity) with shorter follow-up, they found that only one parameter was associated

This article is protected by copyright. All rights reserved.

Accepted Article

with recurrence on stepwise multivariable analysis. However, for their study the predictive variable was LA size and the methodological differences are important. In particular, it is not clear whether atrial volumes were assessed in systole or diastole, and scar was thresholded at IIR 1.20 rather than 0.97, resulting in a much lower median fibrosis burden of 6%. In the absence of a clear gold standard for quantification of atrial fibrosis, and mean fibrosis burdens varying widely in apparently similar patient cohorts (for reference, the mean fibrosis in the DECAAF study was 18.1%[3]), further comparisons between analysis techniques are required.

In this study, LA sphericity demonstrated no association with AF ablation outcome, in contrast to the findings of the original publication [10]. The absence of association with outcome may be related partly to the method of assessment. The Barcelona group assessed sphericity using a non-ECG-gated CMR angiogram acquisition, acquiring in atrial systole or diastole, whereas in this study the sphericity was assessed at a uniform point in the cardiac cycle, in atrial diastole. However, derived sphericity scores for this study and the Barcelona study were very similar (PAF: 81.1±3.2 versus 81.4±2.95 and PersAF: 83.3±3.3 and 82.8±3.4 respectively), as was the reliability of the measure (interobserver concordance correlation coefficient 0.91 versus 0.94, see online supplement). The sphericity index may be more important when assessed in atrial systole, but this is dependent upon imaging in sinus rhythm.

Clinical implementation

The aim of the study was to implement multiple CMR indices for AF recurrence post-ablation, with a view to generating a synergistic, weighted, risk score for future validation, based on all parameters and derived from a single imaging procedure. However, in this patient cohort only LA fibrosis was independently associated with

This article is protected by copyright. All rights reserved.

Accepted Article

outcome. Interobserver variability in measurement was relatively low (see online supplement), but the study may have been underpowered to detect the impact of LAEF, LVEF and indexed LA volume.

The most useful clinical outcome would be a reliable predictor for patients highly unlikely to benefit from a standard ablation procedure. In this study, a fibrosis cut-off of 50% had a positive predictive value for recurrence by six months of 67%, and negative predictive value 79%. However, excluding this high fibrosis cohort would risk 33% of those patients not having a procedure from which they might otherwise derive substantial benefit, and only 17 patients (20%) fell into this high fibrosis group. A CMR-derived prediction of outcome, though, may enable patients to make a decision on the appropriateness of ablation for them based upon the likelihood of long-term freedom from AF, rather than a short-term effect, so long as the uncertainty in the prediction is adequately explained.

Larger studies may show that combining LA fibrosis with other CMR-derived indices improves predictive value. Combination with other CMR indices such as atrial T1 mapping [15], LV scar [16], ventricular post-contrast T1-mapping [17], and PV size [18] may also improve overall performance, but were not investigated in this study. However, a multimodality score is most likely to achieve the highest precision, and other non-invasive non-CMR indices including surface ECG dominant frequency [19] and LA deformation patterns on echocardiography [20] may be combined with invasive characterization such as voltage mapping [21] in order to optimize ablation strategies through the identification of a high-performance biomarker.

This article is protected by copyright. All rights reserved.

Accepted Article

Limitations

This study aimed to implement a 'real-world' assessment of CMR-derived indices, and it is important that limitations should be acknowledged. Firstly, the cohort size, and in particular the number of recurrences (26 (30% of non-censored patients) at 6 months, 31 (40%) at one year, and 37 (64%) at 2years), is small for the evaluation of multiple indices. However, the use of a single center with extended follow-up was important to minimize inter-procedural variations. Criteria for progressing from PVI alone to more extensive ablation strategies were dependent upon patient and electrophysiological findings, and were not determined by CMR indices, but ablation strategies have evolved with time: it is no longer our practice to perform CFE ablation in an effort to terminate AF.

This study has used the most widely employed recurrence definitions, in the context of thorough clinical follow-up, but brief recurrences that may have been captured by more comprehensive monitoring strategies are likely to have been missed.

The method used to quantify atrial fibrosis was derived from that of the Johns Hopkins group, and demonstrated similar average scores and hazard ratio, but has not been independently validated against voltage or histology. Atrial fibrosis quantification remains difficult to reproduce between centers, and it should be noted that some well-designed, rigorous, studies have failed to show an association with outcome[5].

Imaging quality is generally inferior in the presence of arrhythmia, and LAEF in particular varied between sinus rhythm and AF (see online supplement). Furthermore, those in AF during CMR may be more prone to atrial wall movement artefact, and hence inclusion of the atrial blood pool in the atrial wall voxels, artificially increasing

This article is protected by copyright. All rights reserved.

Accepted Article

the fibrosis score. However, a risk stratification method needs to be as inclusive as possible, and elimination of subjects in AF is not generally feasible. Several previous studies of atrial fibrosis have included a proportion of patients in AF (generally 10-30%)[2,3,5,13] DC cardioversion can clearly be coordinated with CMR assessment, but the time-dependent impact of cardioversion on LV and LA function has not been detailed, and the longer the CMR scan is delayed post-cardioversion, the more likely the arrhythmia is to recur.

Conclusion

In this study, the individual and combined predictive value of CMR-derived indices for AF recurrence post-ablation were evaluated. In a real-world cohort, only LA fibrosis was found to be independently associated with outcome. An effective biomarker for AF ablation stratification and tailoring of treatment is required, but this study suggests that CMR can perform only a partial evaluation of the atrial substrate. Combinations of multimodality indices or more sophisticated tissue characterization techniques are required in order to further improve pre-ablation assessment.

Funding Sources

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London, by the NIHR Healthcare Technology Co-operative for Cardiovascular Disease at Guy’s and St Thomas’ NHS Foundation Trust, and by the Cardiovascular HTC.

Disclosures

None

This article is protected by copyright. All rights reserved.

Accepted Article

References

1. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen S-A, Crijns HJG, Damiano RJ, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim Y-H, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao H-M, Wilber D, TASK FORCE MEMBERS:, Chairs:, Section Chairs: Atrial Fibrillation: Definitions, Mechanisms and R for A--, Prystowsky EN, Damiano R, Jackman WM, Marchlinski F, McCarthy P, Document reviewers:, Ad N, Cummings J, Gillinov AM, Heidbuchel H, January C, Lip G, Markowitz S, Nair M, Ovsyshcher IE, Pak H-N, Tsuchiya T, Shah D, Siong TW, Vardas PE. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. *Europace* [Internet]. 2012 [cited 2013 Aug 11];14:528–606. Available from: http://europace.oxfordjournals.org/cgi/doi/10.1093/europace/eus027

2. Oakes RSR, Badger TTJ, Kholmovski EGE, Akoum N, Burgon NS, Fish EN, Blauer JJE, Rao SN, DiBella EVR, Segerson NM, Daccarett M, Windfelder J, McGann CJ, Parker D, MacLeod RS, Marrouche NF. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation* [Internet]. 2009 [cited 2013 Dec 13];119:1758–1767. Available from:

This article is protected by copyright. All rights reserved.

Accepted Article

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2725019&tool=pmcentrez&rendertype=abstract

3. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B, Daoud E, Wissner E, Bansmann P, Brachmann J, Investigation O. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* [Internet]. 2014 [cited 2014 Apr 15];311:498–506. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24496537

4. Khurram IM, Beinart R, Zipunnikov V, Dewire J, Yarmohammadi H, Sasaki T, Spragg DD, Marine JE, Berger RD, Halperin HR, Calkins H, Zimmerman SL, Nazarian S. Magnetic resonance image intensity ratio, a normalized measure to enable interpatient comparability of left atrial fibrosis. *Hear Rhythm* [Internet]. 2014 [cited 2014 Feb 21];11:85–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24096166

5. Sramko M, Peichl P, Wichterle D, Tintera J, Weichet J, Maxian R, Pasnisinova S, Kockova R, Kautzner J. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. *Int J Cardiol* [Internet]. 2015;179:351–357. Available from: http://dx.doi.org/10.1016/j.ijcard.2014.11.072

6. Dodson JA, Neilan TG, Shah R V., Farhad H, Blankstein R, Steigner M, Michaud GF, John R, Abbasi SA, Jerosch-Herold M, Kwong RY. Left atrial passive

This article is protected by copyright. All rights reserved.

Accepted Article

emptying function determined by cardiac magnetic resonance predicts atrial fibrillation recurrence after pulmonary vein isolation. *Circ Cardiovasc Imaging*. 2014;7:586–592.

7. den Uijl DW, Cabanelas N, Benito EM, Figueras R, Alarcón F, Borràs R, Prat S, Guasch E, Perea R, Sitges M, Brugada J, Berruezo A, Mont L. Impact of left atrial volume, sphericity, and fibrosis on the outcome of catheter ablation for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2018;29:740–746.

8. Habibi M, Lima JAC, Gucuk Ipek E, Zimmerman SL, Zipunnikov V, Spragg D, Ashikaga H, Rickard J, Marine JE, Berger RD, Calkins H, Nazarian S. The association of baseline left atrial structure and function measured with cardiac magnetic resonance and pulmonary vein isolation outcome in patients with drug-refractory atrial fibrillation [Internet]. Hear. Rhythm. 2016;13:1037–1044. Available from: http://dx.doi.org/10.1016/j.hrthm.2016.01.016

9. Balk EM, Garlitski AC, Alsheikh-Ali A a, Terasawa T, Chung M, Ip S. Predictors of atrial fibrillation recurrence after radiofrequency catheter ablation: a systematic review. *J Cardiovasc Electrophysiol* [Internet]. 2010 [cited 2014 Sep 20];21:1208–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20487117

10. Bisbal F, Guiu E, Calvo N, Marin D, Berruezo A, Arbelo E, Ortiz-Pérez J, De Caralt TMM, Tolosana JM, Borràs R, Sitges M, Brugada J, Mont L. Left atrial sphericity: a new method to assess atrial remodeling. Impact on the outcome of atrial fibrillation ablation. *J Cardiovasc Electrophysiol* [Internet]. 2013 [cited

This article is protected by copyright. All rights reserved.

Accepted Article

2014 May 27];24:752–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23489827

11. McLellan AJA, Ling LH, Ruggiero D, Wong MCG, Walters TE, Nisbet A, Shetty AK, Azzopardi S, Taylor AJ, Morton JB, Kalman JM, Kistler PM. Pulmonary vein isolation: The impact of pulmonary venous anatomy on long-term outcome of catheter ablation for paroxysmal atrial fibrillation. *Hear Rhythm* [Internet]. 2014;11:549–556. Available from: http://dx.doi.org/10.1016/j.hrthm.2013.12.025

12. O'Neill MD, Jaïs P, Takahashi Y, Jönsson A, Sacher F, Hocini M, Sanders P, Rostock T, Rotter M, Pernat A, Clémenty J, Haïssaguerre M. The stepwise ablation approach for chronic atrial fibrillation - Evidence for a cumulative effect. *J Interv Card Electrophysiol*. 2006;16:153–167.

13. Khurram IM, Habibi M, Gucuk Ipek E, Chrispin J, Yang E, Fukumoto K, Dewire J, Spragg DD, Marine JE, Berger RD, Ashikaga H, Rickard J, Zhang Y, Zipunnikov V, Zimmerman SL, Calkins H, Nazarian S. Left Atrial LGE and Arrhythmia Recurrence Following Pulmonary Vein Isolation for Paroxysmal and Persistent AF. *JACC Cardiovasc Imaging* [Internet]. 2015 [cited 2016 Aug 1];9:142–148. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1936878X15009638

14. Habibi M, Lima JAC, Khurram IM, Zimmerman SL, Zipunnikov V, Fukumoto K, Spragg D, Ashikaga H, Rickard J, Marine JE, Calkins H, Nazarian S. Association of left atrial function and left atrial enhancement in patients with atrial

This article is protected by copyright. All rights reserved.

Accepted Article

fibrillation cardiac magnetic resonance study. *Circ Cardiovasc Imaging*. 2015;8:e002769.

15. Beinart R, Khurram IM, Liu S, Yarmohammadi H, Halperin HR, Bluemke DA, Gai N, van der Geest RJ, Lima JACC, Calkins H, Zimmerman SL, Nazarian S. Cardiac magnetic resonance T1 mapping of left atrial myocardium. *Hear Rhythm* [Internet]. 2013;10:1325–31. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1547527113005110

16. Neilan TG, Shah R V., Abbasi SA, Farhad H, Groarke JD, Dodson JA, Coelho-Filho O, McMullan CJ, Heydari B, Michaud GF, John RM, Van Der Geest R, Steigner ML, Blankstein R, Jerosch-Herold M, Kwong RY. The incidence, pattern, and prognostic value of left ventricular myocardial scar by late gadolinium enhancement in patients with atrial fibrillation. *J Am Coll Cardiol*. 2013;62:2205–2214.

17. McLellan AJA, Ling LH, Azzopardi S, Ellims AH, Iles LM, Sellenger MA, Morton JB, Kalman JM, Taylor AJ, Kistler PM. Diffuse ventricular fibrosis measured by T1 mapping on cardiac MRI predicts success of catheter ablation for atrial fibrillation. *Circ Arrhythmia Electrophysiol*. 2014;7:834–840.

18. Hauser TH, Essebag V, Baldessin F, McClennen S, Yeon SB, Manning WJ, Josephson ME. Prognostic value of pulmonary vein size in prediction of atrial fibrillation recurrence after pulmonary vein isolation: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* [Internet]. 2015;17:49. Available from: http://jcmr-

This article is protected by copyright. All rights reserved.

Accepted Article

online.biomedcentral.com/articles/10.1186/s12968-015-0151-z

19. Lankveld T, de Vos CB, Limantoro I, Zeemering S, Dudink E, Crijns HJ, Schotten U. Systematic analysis of ECG predictors of sinus rhythm maintenance after electrical cardioversion for persistent atrial fibrillation. *Hear Rhythm* [Internet]. 2016;13:1020–1027. Available from: http://dx.doi.org/10.1016/j.hrthm.2016.01.004

20. Montserrat S, Gabrielli L, Bijnens B, Borras R, Berruezo A, Poyatos S, Brugada J, Mont L, Sitges M. Left atrial deformation predicts success of first and second percutaneous atrial fibrillation ablation. *Hear Rhythm* [Internet]. 2015;12:11–18. Available from: http://dx.doi.org/10.1016/j.hrthm.2014.08.032

21. Kosiuk J, Dinov B, Kornej J, Acou WJ, Schonbauer R, Fiedler L, Buchta P, Myrda K, Gasior M, Poloñski L, Kircher S, Arya A, Sommer P, Bollmann A, Hindricks G, Rolf S. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. *Hear Rhythm*. 2015;12:2207–2212.

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* [Internet]. 1987 [cited 2017 Mar 7];40:373–383. Available from: http://linkinghub.elsevier.com/retrieve/pii/0021968187901718

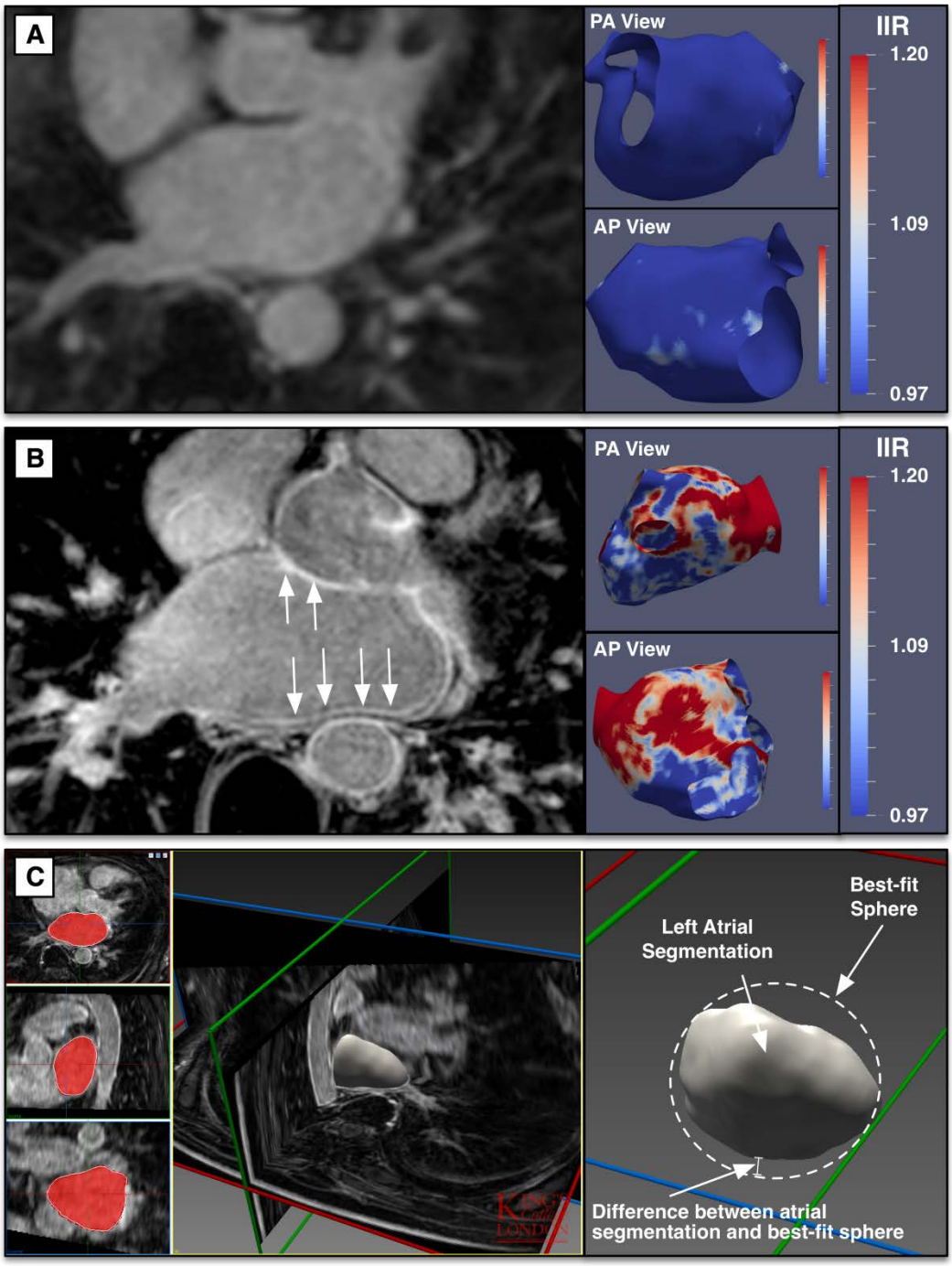
This article is protected by copyright. All rights reserved.

Accepted Article

Figures

Figure 1. Illustration of left atrial fibrosis quantification and sphericity assessment.

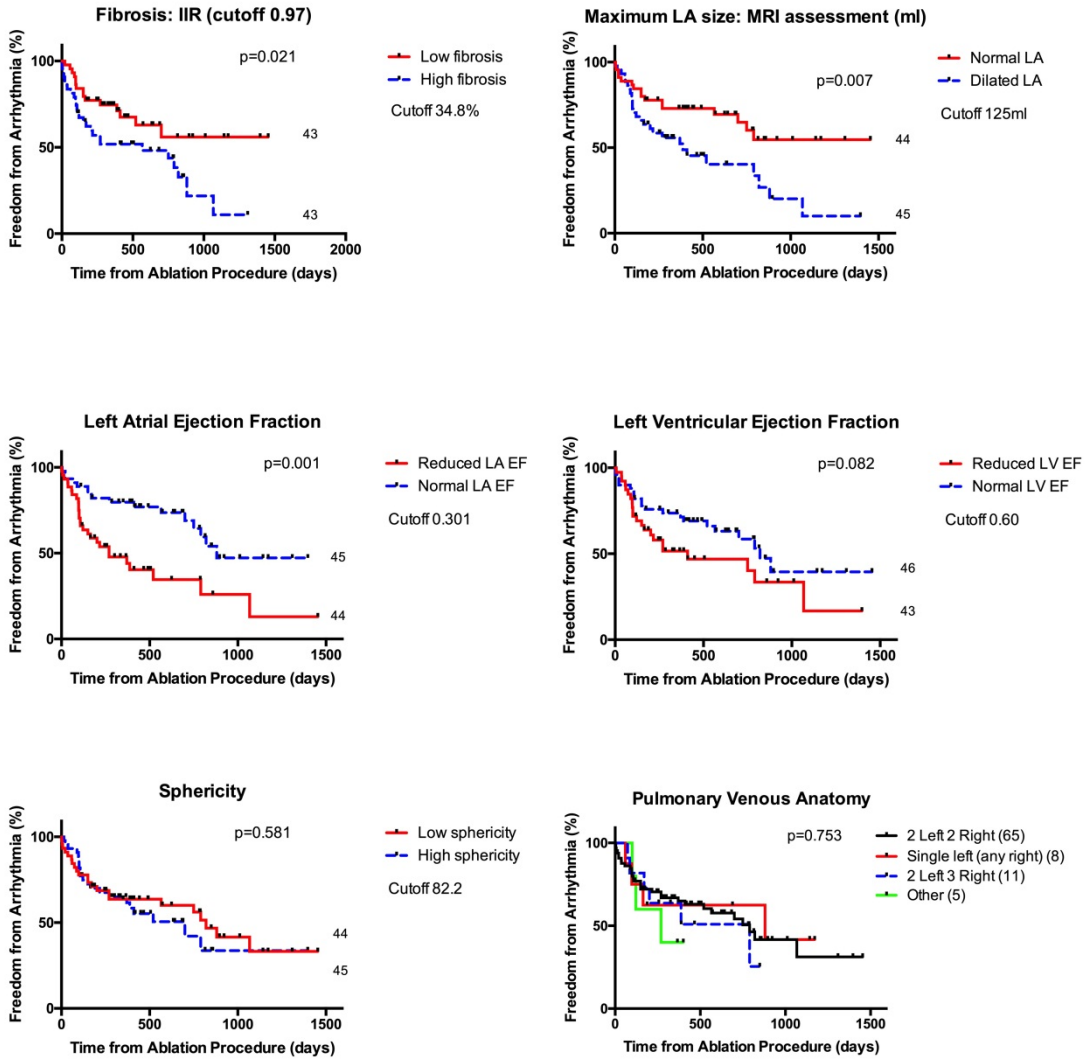
(A) Low fibrosis left atrium (LGE-18% (left)), with atrial shell thresholded at image intensity ratio (IIR) 0.97. (B) High fibrosis left atrium (74%), white arrows indicating regions of LA wall enhancement (C) (Left) multiplanar reconstruction of 3D LGE dataset, with LA body-only segmentation, and (right) sphericity calculation. For this subject, sphericity was 88.6%.



This article is protected by copyright. All rights reserved.

Figure 2. Kaplan Meier survival curves for CMR indices.

Each parameter has been dichotomised (except pulmonary vein anatomy). Number of subjects in each group at the start of follow-up shown at the end of the curve (total =89 in all plots except fibrosis, where n=86).

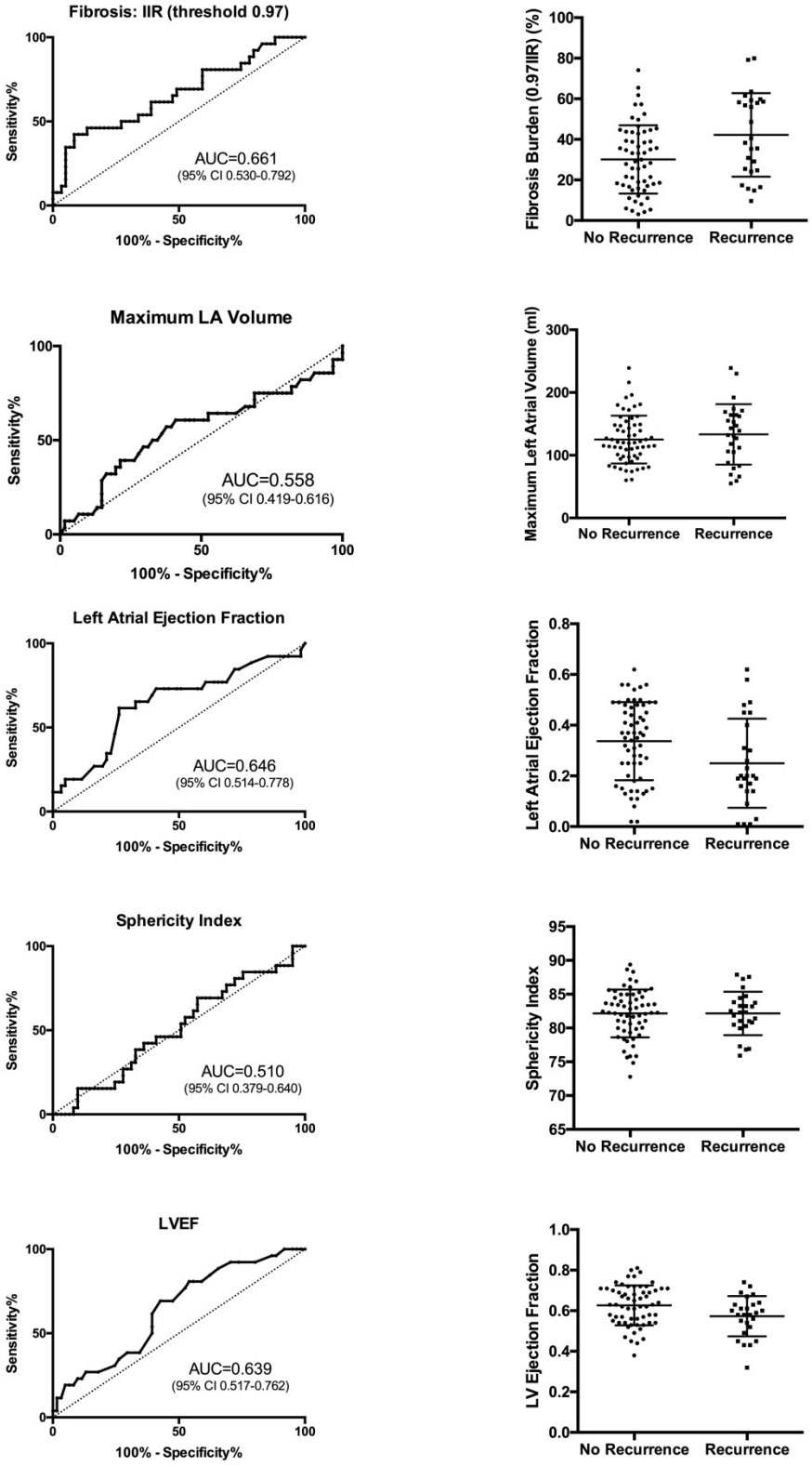


This article is protected by copyright. All rights reserved.

Accepted Article

Figure 3. Receiver operator characteristic curves (left sided panels) and index distribution between subjects with recurrence and no recurrence (right sided panels) at 150days post procedure.

AUC: Area under curve. CI: confidence interval



This article is protected by copyright. All rights reserved.

Accepted Article

Tables

Table 1. Baseline demographics and findings.

Hazard ratios calculated on univariate Cox regression analysis. AF: atrial fibrillation, BMI: body mass index. Significant comorbidity defined as Charlson comorbidity index ≥ 1 22

	All Subjects (n=89)	**Hazard ratio for AF recurrence (95% CI)**	**p-value**
Male Sex	65 (73%)	1.34 (0.67-2.7)	0.40
Non-paroxysmal AF	41 (47%)	2.3 (1.25-4.3)	0.008
AF duration (years)	3.9 (IQR 2.0-5.0)	1.05 (0.98-1.12)	0.17
Significant Comorbidities	26 (29%)	1.02 (0.56-1.88)	0.92
Hypertension	23 (26%)	0.87 (0.43-1.78)	0.71
Ischaemic Heart Disease	7 (8%)	1.51 (0.53-4.2)	0.43

This article is protected by copyright. All rights reserved.

Accepted Article

Age (years)	59.6 ±11.0	1.007 (0.98-1.03)	0.59
Weight (kg)	88.4±15.9	0.999 (0.98-1.02)	0.93
BMI (kg/m^2)	28.7±4.8	0.97 (0.91-1.03)	0.34
LV Mass (g) on CMR	111±31	0.995 (0.98-1.004)	0.30
Native ventricular T1 relaxation time (msec)	991±42	0.996 (0.99-1.004)	0.34
AF during CMR	36 (40%)	2.2 (1.20-4.1)	0.011

Table 2. CMR-derived indices by recurrence group at one year.

	All Subjects (n=89)	**No Recurrence (n=58)**	**Recurrence (n=31)**	**Hazard Ratio (95% CI)**	**p-value**

This article is protected by copyright. All rights reserved.

Accepted Article

LA fibrosis (%)	33.5±18.8	29.0±16.9	41.8±19.3	1.032 (1.013-1.052)	0.002
Maximum LA Volume (ml)	127±41	124±38	135±47	1.008 (1.000-1.015)	0.048
LA ejection fraction (%)	30.9±16.5	33.8±15.8	25.4±16.8	0.063 (0.006-0.594)	0.016
LV ejection fraction (%)	60.7±10.3	62.9±10.1	56.7±9.0	0.011 (0.0004-0.303)	0.008
LA sphericity	82.1±3.4	82.2±3.5	81.9±3.2	0.975 (0.882-1.08)	0.62
Single left sided pulmonary vein	8 (9%)	5 (6%)	3 (10%)	1.11 (0.34-3.67)	0.86

This article is protected by copyright. All rights reserved.

Accepted Article

Table 3. Multivariable Cox regression analysis of the association of established CMR indices with arrhythmia recurrence.

For Model 1 and 2, each row represents a separate multi-variable analysis. Model 1 is adjusted for age and sex alone, Model 2 additionally for AF type (binary: PAF/non-PAF). Model 3 contains all factors of Model 2, and the three significant CMR derived indices, in a single multivariate analysis. EF: ejection fraction, HR: Hazard Ratio, CI: confidence interval.

	Model 1			**Model 2**			**Model 3**		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Non-paroxysmal AF	NA	NA	NA	2.24	1.19-4.2	**0.01**	1.49	0.75-2.9	0.25

This article is protected by copyright. All rights reserved.

Accepted Article

Fibrosis (%)	1.027	1.009-1.044	**0.002**	1.024	1.006-1.042	**0.009**	1.021	1.003-1.040	**0.022**
LA Volume (ml)	1.007	0.999-1.015	0.07	1.004	0.996-1.011	0.37	-	-	-
LA EF	0.042	0.005-0.317	**0.002**	0.077	0.008-0.732	**0.026**	0.193	0.012-3.10	0.25
LV EF	0.016	0.001-0.340	**0.008**	0.031	0.001-0.821	**0.037**	0.126	0.003-5.26	0.28
Sphericity	0.996	0.909-1.091	0.93	0.956	0.873-1.046	0.33	-	-	-
Single left-sided pulmonary vein	1.129	0.805-1.585	0.48	1.062	0.753-1.497	0.73			

This article is protected by copyright. All rights reserved.

Table 4. Classification table for binomial logistic regression analysis of arrhythmia recurrence at six months

		Predicted		
		No Recurrence	Recurrence	Percentage Correct
Outcome	No Recurrence	55	3	Specificity 95%
	Recurrence	15	11	Sensitivity 42%
		Negative predictive value 79%	Positive predictive value 79%	Accuracy 78.6%

Accepted Article

This article is protected by copyright. All rights reserved.